COMPARATIVE STUDIES OF DIFFERENT CLOBETASOL PROPIONATE LOADED NANO CARRIER TOPICAL SYSTEMS FOR MANAGEMENT OF PSORIASIS

A

RESEARCH PROPOSAL

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DISCIPLINE PHARMACEUTICS

By

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Title:

Comparative studies of different clobetasol propionate loaded nano carrier topical systems for management of psoriasis.

Introduction:

Psoriasis is a long-lasting autoimmune disease characterized by patches of abnormal skin. These skin patches are typically red, itchy, and scaly. They may vary in severity from small and localized to complete body coverage. Injury to the skin can trigger psoriatic skin changes at that spot, which is known as Koebner phenomenon. (Afifi et al., 2005)

There are five main types of psoriasis:

plaque, guttate, inverse, pustular, and erythrodermic (Menter et al., 2008)

Epidermiology:

- Psoriasis, a chronic proliferative skin disease is one of the most common immune mediated disorders occurring in 1.5 – 3 % of population world wide. Of patients, 75% present with symptoms of psoriasis before age 45yrs.(Cox et al., 2010)
- Although rarely life-threatening, psoriasis has an adverse physical and emotional impact on quality of life. (Fisher, 2004)
- Prevalence rates are extremely high in aboriginal tribes in Australia, Africa, south America, and other developing regions of the world.
- In 2009 retrospective study of 30,078 children in India, was found to be the second most common skin disease in all age groups of children, and the third most common skin disease infants.

Literature Review:

Available treatment strategies

Generally, treatment choices for psoriasis involve three main modes namely topical therapy, phototherapy and systemic therapy. For psoriasis treatment topical therapies are considered first. Phototherapy is suggested in case of non-effectiveness of topical therapy or

relentlessness of the psoriasis condition, which is followed by systemic medications as shown in Table 1.

Phototherapy and systemic agents exhibit numerous ill effects such as hepatotoxicity, renal toxicity, hypertension, hyperlipidemia and skin cancer. Moreover the currently available treatments based on conventional formulation for psoriasis are associated with problems like increased dosing frequency, increased side effects and decreased safety profile for long term use.

Topical	Tars	Tar
	Antracens	Dithranol
	Psoralens	Trioxysalen – Methoxsalen
	Others	Fumaric acid – vitamin D (Calcipotriol, Tacalcitol, Calcitriol) – Tazarotene
Phototherapy		Artificial or natural light sources
Systemic	Psoralen	Methoxsalen – Bergapten- Trioxysalen
	Retinoids	Etretinate – Acitretin

Table 1: Available Treatment Strategies for Psoriasis

Among the currently available treatments, none of the treatment for psoriasis is found to be safe, effective and able to completely cure the disease. Further, available treatment options are associated with both inappropriate cosmetic appearance and related toxicities leading to poor patient compliance in long term use. Therefore development of an ideal therapy for psoriasis is a great challenge. The lack of effective and safe treatment for psoriasis has created needs to develop and implement novel approach with a view to make the therapy more useful and acceptable. To overcome the drawbacks of conventional dosage forms, formulation development is aimed to design drug cargo exhibiting ease of administration, reduced dosing frequency, and sustained release for improved therapeutic benefit to psoriatic patients.

Challenges for topical drug delivery in psoriatic skin conditions

Although topical drug delivery offers certain advantages over systemic delivery for selected drugs and conditions, the resistance against drug transport across skin barrier remains a major challenge to efficient drug delivery by this route. There is also potential of skin irritation or contact dermatitis arising from one or more components in the topical formulation. In some cases poor permeability of some drugs through the skin leads to poor pharmacological response. Possibility of allergic reactions and degradation of drug by the enzymes present in epidermis may create problems.

Rigidization of psoriatic skin has been attributed to a rise in the levels of cholesterol and fall in the levels of ceramides. Apart from this, normal moisturizing factors (NMFs) like water are almost absent in the psoriatic skin of a patient. As a result of these factors, targeting drug molecule in a vehicle to the psoriatic tissues using topical route poses a big challenge.
Common skin changes in psoriasis are:

- Skin lesions covered with scales having thickened inflammation.
- Dry skin due to deficient natural moisturizing factor
- Imbalanced skin lipids
- Skin having tethered hair
- Skin sensitivity
- Corneocytes have excessive growth and aberrant differentiation

The application of lipids in particular in the formulations can resolves the problem of lipid imbalance and lack of moisture content. Thus, the lipoidal and allied carriers can result in an effective delivery of drugs across psoriatic skin.

3.5 Novel Colloidal Drug Delivery Systems

Novel drug delivery systems are aimed at achieving improved therapeutic benefit of existing drugs as well as safe and effective delivery of new drugs to meet the spatial and temporal needs of the body. Colloidal drug delivery systems (CDDS) are particulate or vesicular dosage having size range from 1 nm to 0.5 μm. They sequester, transport and retain the active drug to deliver it at its site of action.

Due to the low penetration and/or low stability of the bioactive species (drug) in the skin, they are commonly associated with nanostructures to enhance their effectiveness. Moreover, the reduced size of nanocarriers allows their interaction with cells and subcellular

structures, including macromolecules. Vesicle nanocarriers, such as liposomes, nanosomes, niosomes, ethosomes and transfersomes, are the most commonly used systems in cosmetic applications because they may incorporate hydrophobic species, improving the stability and skin tolerance of ingredients, contributing to the safety of cosmetics. Nanoemulsions, nanocapsules and nanospheres have been shown to favor the topical administration of active compounds, mainly due to their increased performance in terms of skin hydration, transparency and sensation to touch. However, important features such as the controlled release of lipophilic substances, increased adhesiveness of the bioactive substance when in contact with the skin, increased compound-loading capacity, and higher stability during storage have been achieved with these nanocarriers.

Various novel carriers with their merits, drawbacks, marketed and clinical trial products are listed in Table 2.

Table 2: List of novel colloidal carriers and their marketed products

S. no.	**Novel based carrier system**	**Advantages**	**Limitations**	**Product**	**Marketed/ clinical trial**
1	Microspheres	Cheaply prepared, can be administered by s.c., i.m., intra peritoneal (i.p.) route, thus implantation not needed.	Burst effect i.e. premature drug release, poor drug entrapment, rapidly taken by reticulo endothelial system (RES).	Arestin	Marketed
2	Liposphere	Biocompatible, amphiphilic nature.and surface modification is easy.	Weak loading capacity, rapid drug leakage, limited physical and chemical stability during storage.	AmBisome®, DaunoXome®, Pevaryl®, Myoset.	Marketed

3	Polymeric nanoparticle	Biocompatible, biodegradable and numerous classes of drugs can be entrapped.	Polymer toxicity, difficulty of the large-scale production.	Decapeptyl ®, Gonapeptyl Depot ®, Enantone Depot ®, Abraxane.	Marketed
4	Solid lipid nanoparticle	Biocompatible, biodegradable, higher efficacy, flexibility of size and surface manipulation.	Poor stability, poor batch to batch reproducibility, sterilization difficulties, low drug loading.	Nanobase, nanopearl.	Marketed
5	Nanolipid carriers	Biodegradable increases the drug payload and reduces expulsion of the drug during storage.	Sterilization difficulties.	NLC repair cream, NLC reconstruction cream.	Marketed
6	Micelle	Self-assembling, thermodynamic stability and targeting potential.	Not good for hydrophilic drugs.	Genexol PM, NK105: Phase I, NK911: Phase I.	Marketed and clinical trial
7	Dendrimers	Ease of preparation and modification.	Polymer dependent biocompatibility.	Dendritech TM, Astromol TM.	Marketed
8	Liposome	Biocompatible, ease of surface modification and amphiphilic nature.	Weak loading capacity, rapid drug leakage, limited physical and chemical stability during storage.	AmBisome®, Doxil/Caelyx, Myoset, DaunoXome Cisplastin: Phase I/II.	Marketed and clinical trial

9	Niosome	Improves the bioavailability of inadequately absorbed drugs (oral) and increases the penetration power of drugs through skin.	Less skin penetration, do not reach up to deeper skin layer.	Lancome, Dorzox, Novasome.	Marketed
10	Transferosome	Non-invasive delivery of large molecular weight drugs on the skin.	Chemically unstable, very expensive.	Actrapid, Novo, Nordis, Transfersulin, Directin: Phase III.	Marketed/ clinical trial
11	Sphingosome	Increased stability, increase efficacy and therapeutic index.	Low entrapment efficacy, high cost of sphingolipids.	Marqibo™, Oncovin TM, Navelbine(R), Hycumtin(R).	Marketed
12	Ethosome	Very good permeation power, high patient compliance. Composition is safe for dermal and pharmaceutical use.	Poor yield.	Noicellex TM, Lipoduction TM, Nanominox©.	Marketed
13	Phytosomes	Greater therapeutic effect, better bioavailability in oral and transdermal route.	Low stability.	Silybin, Gingko, Olive oil pyhtosomes.	Marketed

Selection of delivery systems

Nanotechnology based drug delivery system has immense potential to enhance the bioavailability and effectiveness of drugs in their dosage forms, especially lipophilic drugs. The most widely used drug delivery systems include lipid based nanoparticles i.e. nanoemulsions, solid lipid nanoparticles, lipid nanocapsules, nanosuspension, liposomes,

liquid crystalline nanoparticles, lipid-drug conjugates) or polymer based nanocarriers (polymeric nanoparticles, polymeric micelles, polymer-drug conjugates).

The existence of squalene and fatty esters in the squarticles increases the drug uptake into sebaceous glands. These components have affinity towards the sebum, carrying the drug to form a reservoir in the pilosebaceous glands.SPC in the nanoparticulate system also played an important role for enhancing follicular targeting. Deformable liposomes are elastic, flexible liposomes represent a novel type of phospholid vesicles designed to improve dermal permeability and retention of drug at sebaceous gland.(Aljuffali et al., 2014)

NLC

Nanostructured lipid carriers (NLC) are a delivery system in which partial-crystallized lipid particles with mean radii ≤ 100 nm are dispersed in an aqueous phase containing emulsifier(s), as a potential delivery system may have some advantages in certain circumstances when compared with other colloidal carriers.(Hamishehkar et al., 2015)

Nano emulsions

Nano emulsions are non-toxic lipid droplets a few hundred nanometers in diameter and made from surfactants approved for human consumption and common food substances that are 'Generally Recognized as Safe' (GRAS) by the FDA. These emulsions are easily produced in large quantities by mixing a water-immiscible oil phase into an aqueous phase with a high-stress, mechanical extrusion process that is available worldwide. (Khandavilli and Panchagnula, 2007)

Deformable liposomes

Delivery of clobetasol to hair follicles and related cells is important in the treatment of psoriasis. Here we report the development of nanoparticles formed from sebum-derived lipids such as squalene and fatty esters, for use in achieving targeted drug delivery to the sebaceous glands. Three different Nano systems, nanostructured lipid carriers (NLC) and Nano emulsions (NE) and deformable liposomes were prepared.(Patel et al., 2010)

These Nano systems have great potential for transdermal drug delivery. In this study, nanostructured lipid carriers (NLCs), Nano emulsions and deformable liposomes were prepared by using sebum derived lipids to enhance percutaneous permeation. Optimized Nano system formulations were evaluated using uniform design experiments. Nanostructured in vitro transdermal delivery characteristics of antipsoriatic drug loaded NLCs, Nano

emulsions and deformable liposomes were compared using animal skin and human cadaver skin also in vitro studies. Nanoparticle integrity during transdermal delivery and effects on the skin surface were also investigated.(Vincent et al., 2014)

While no cure is available for psoriasis, many treatment options exist. Topical agents are used for treating psoriasis because they produce targeted action.

RATIONALE OF DRUG:

IDEAL REQUIREMENTS OF DRUGS OF SEBACEOUS GLAND DELIVERY:

- ✓ Drug should be lipophilic in nature.
- ✓ The drug should have a molecular weight <500 Daltons to allow skin absorption.
- ✓ Log P ≥1and <4
- ✓ pKa <8 to avoid skin irritation

CLOBETASOL PROPIONATE:

- ❖ Clobetasole propionate has log p of 3.49.
- ❖ water solubility is 0.00413mg/ml at 25◦c.
- ❖ Molecular weight is 466.77g/mol.
- ❖ Melting point 226 ◦c
- ❖ U.V. range 239 nm

Clobetasol propionate is a very potent topical corticosteroid class compound. Topical steroids are used in addition to moisturizers for treating inflammatory skin conditions such as eczema and dermatitis. Owing to its anti-inflammatory, antipruritic and immune-modulating properties, clobetasol propionate is used to treat psoriasis (Decroix et al., 2004). Clobetasol propionate induces phospholipase A2 inhibitory proteins, thereby controlling the release of the inflammatory precursor arachidonic acid from membrane phospholipids by phospholipase A2 (Schäfer-Korting et al., 2005). It was also found that if clobetasol propionate (CP) was incorporated in the nanoemulsion it shows significant increase in their anti-inflammatory activity. It was reported that CP-loaded nanoemulsion significantly increased NTPDase (Nucleoside triphosphate diphosphohydrolases) activity in lymphocytes. This membrane protein is responsible for the hydrolysis of extracellular ATP (Adenosine triphosphate) which

is responsible for cell proliferation, differentiation and inflammatory processes (Alam et al., 2013).

Research Issues/gaps:

- Psoriasis is an **autoimmune disorder** of the skin characterized by relapsing episodes of inflammatory lesions and hyperkeratosis plaque.
- Available treatment options of psoriasis are associated with **inappropriate cosmetic appearance, related toxicities and poor penetration** of conventional carrier system in psoriatic skin; leading to poor patient compliance in long term use.
- Moreover, the drugs which are currently available produce **severe toxic effects** upon prolonged usage.

Problem formulation:

- There is a list of drugs used to treat psoriasis which include Methotrexate, Cyclosporin, Clobetasol propionate, Calcipotriol, Betamethasone, Tazarotene, Temoporfin, Tretinoin etc. Application of high dose of these drugs using conventional formulations creates toxicity and other difficulties so that to minimize these hazards novel drug delivery systems (NDDS) are preferred.
- The novel drug delivery systems will enhance the penetration through psoriatic barriers but we also want their retention in skin so that they do not pass into systemic circulation and causes toxicity. So, to improve the targeting effects, squalene is used as a lipid in novel drug delivery systems (NDDS) because it has affinity towards sebaceous glands.

Research Objectives:

1. To increase the therapeutic effectiveness of antipsoriatic drug.
2. Increase permeation through psoriatic barrier cells.
3. Sebaceous glands utilised as a depot for sustained release of the drug.
4. Minimum absorption in systemic circulation hence side effects are minimised.

Contribution and need of the proposed Research:

To overcome the drawbacks of conventional dosage forms, formulation development is aimed to design drug product exhibiting ease of administration, higher penetration, reduced dosing frequency and sustained release for improved therapeutic benefit to psoriatic patients. Psoriasis is known to have a negative impact on the quality of life of both the affected person and the individual's family members. Thus, it becomes necessary to treat it.

Methodology:

In this research work, it is hypothesized that this system will improve drug deposition in the skin as sebum derived lipid are used which shows affinity towards sebum, these nanosystems enhance drug penetration through the keratinized psoriatic skin cells because of their flexible nature. As the drug deposit in hair follicles it will minimize absorption in the systemic circulation, as a result systemic side effects will be minimized.(Aljuffali et al., 2014)

PLAN OF WORK

Preformulation Studies

- ✓ Physical Appearance
- ✓ Melting Point Determination
- ✓ UV Spectroscopy
- ✓ Solubility Analysis
- ✓ IR Spectroscopy

Development and optimization of Nanosystems

- ✓ Preparation of nanosystems
- ✓ Optimization and evaluation of Novel carrier systems
- ✓ Particle size & polydispersity index of Novel carrier systems.
- ✓ Drug loading and encapsulation efficiency measurement.

In vitro drug release study :

- ✓ Dialysis membrane
- ✓ Release kinetics
- ✓ Percentage retain on surface.
- ✓ Drug penetration study
- ✓ Drug retention study

- ✓ Comparison with marketed Topinate gel (systopic laboratories pvt. ltd.)

***In vivo* studies** on mice using IMQ-induced psoriatic-like plaque for evaluation of delivery systems

- ✓ Skin irritation test
- ✓ Pharmacokinetic studies
- ✓ Histopathology

Technology Selection:

Novel carrier systems (Nanoemulsions, Nanostructured lipid carriers, Deformable liposome)

Modifications

As we are using squalene in our preparation (Nanostructured lipid carrier and nanoemulsion) in lipidic phase so it will provide depot effect at pilosebaceous glands and in case of deformable liposome; because of their flexible nature they passes through psoriatic barrier skin cells. These systems show minimum absorption in systemic circulation hence side effects are minimized.

Place of Work: I.S.F. College of Pharmacy, Moga

Resources (Hardware/Software/) required & availability status:

Sr.No.	Resources	Availability
1.	**HPLC**	I.S.F. College of Pharmacy, Moga
2.	**UV Spectrophotometer**	I.S.F. College of Pharmacy, Moga
3.	**Zeta Sizer**	I.S.F. College of Pharmacy, Moga
4.	**Homogenizer**	I.S.F. College of Pharmacy, Moga
5.	**Sonicator**	I.S.F. College of Pharmacy, Moga
6.	**TEM**	External Source
7.	**SEM**	External Source
8.	**DSC**	External Source
9.	**Histopathology**	External Source

Extent of External Assistance Required (if any):

TEM, SEM, DSC and Histopathology require external assistance

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